UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/736,076	12/13/2000	Shmuel A. Ben-Sasson	1242.1015-009	6540

1444 7590 11/19/2003

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER
AUDET, MAURY A

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/736,076	BEN-SASSON, SHMUEL A.	
	Examiner	Art Unit	
	Maury Audet	1654	

-- Th MAILING DATE f this communication app ars n th cover she t with th correspondence addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *40 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39, 42-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2 IDS's* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group III, claim 42, in the response of 9/12/03 is acknowledged. Applicant's Supplemental Amendment of 11/12/03 (by fax) is also acknowledged, canceling claims 40-41, amending claim 1-39 to depend from claim 42 and adding new claims 43-50 to depend from claim 42. Applicant has stated on page 30 of the Supplemental Amendment that "Note that new claims 43-50 are directed to the use of the peptides that were allowed in patent no. 6,174,993, that issued from the parent application no. 08/861,338 [and] [a]s all of the claims are directed to the elected Group III, it is urged that all be examined and allowed in this case." "It is well settled that whether similar claims have been allowed to others is immaterial." *In re Giolito*, 530 F.2d 397, 188 USPQ 645 (1976). Particularly since completely updated searches will need to be submitted/analyzed in order to determine patentability as to any later filed application, including continuations. This is because applications which may have been filed and pending before Applicant's priority application, may have contained compounds/sequences that were not yet submitted/present in compound databases (STN/CAS) or in sequence compliance (and thus not entered into sequence databases) at the time Applicant's similar case/claims were allowed. Additionally, whether a previous Examiner was willing to search/examine distinctly different compounds/sequences, that each required separate search/examination, is also immaterial.

In the present case, Applicant's still has not elected a specific peptide, as the elected invention, as required by the restriction requirement. Therefore, Applicant's response to the restriction is *unresponsive*. However, *in order to move the prosecution forward*, this Examiner

has searched and herein examines SEQ ID NOS: 15-19 (5) (claim 49), as drawn to the elected invention Group III, since these five sequences were found to have a recognizable core sequence (although only 3 amino acids residues (Pro-Pro-Phe); and notwithstanding the substitution of Lys with Arg at residue 5 in SEQ ID NOS: 16 and 17 and that separate search/analysis of each sequence was still required). Thus, claims 1-39 and 42-50, as drawn to SEQ ID NOS: 15-19 (5) are pending. Claims 40-41 are withdrawn as being cancelled.

Specification

The abstract of the disclosure is objected to because of the following spelling mistakes:

Page 2, line 7 "theonine", needs to be amended to "threonine".

Page 2, line 9, "drivative", needs to be amended to "derivative".

Correction is required. See MPEP § 608.01(b).

Appropriate correction is required.

Claim Objections

Claim 1 is objected to because of the following informalities: deletion of "according" is required.

Claim Rejections - 35 USC § 112 1st Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-39 and 42-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for the use of peptide SEQ ID NOS: 15-19, in a method for modulating the activity of a serine/threonine kinases in a subject, for the following reasons:

The nature of the invention: The claimed invention is drawn to a method for modulating the activity of a serine/threonine kinases in a subject comprising administering a therapeutically effective amount of a peptide comprising a peptide *derivative* of the HJ loop of a serine/threonine kinase, wherein the peptide used may be residues one through 10 of the HJ loop

found among the family of serine/threonine kinases (Fig. 1) OR residues one through 20 of the HJ loop cyclic AMP dependent protein kinase and protein kinase (Fig. 2)(see claim 42), or any peptide derivative thereof where "any one amino acid residue in the peptide can vary, being any naturally occurring amino acid or analog thereof (see for example claim 8).

The state of the prior art and the predictability or lack thereof in the art: The art teaches that a single amino acid substations can alter the antigen-binding specificity of peptides, and thus alter peptide function either in vitro or in vivo (i.e. "in a subject") (Rudikoff et al., Proc Natl Acad Sci U S A. 1982 Mar;79(6):1979-83, page 1979, and page 1982, 1st s. under "Implications for Generation of Diversity").

Additionally:

> The art teaches that the efficacy of therapeutics is dependent upon factors such as solubility of the drug, bioavailability at the target site, attainment of effective plasma concentrations, solubility in tissues, biotransformation, toxicity, proteolytic degradation, immunological inactivation, rate of excretion or clearance (half-life), deactivation by the liver, hydrolysis in serum, binding to plasma protein, and in the case of antivirals, propensity for emergence of resistant strains (see Benet et al., pp. 3-32, in The Pharmacological Basis of Therapeutics, 8th ed., 1990, page 3, first paragraph; page 5, second column, last partial paragraph, first two sentences; page 10, the paragraph bridging columns 1 and 2; page 18, the paragraph bridging columns 1 and 2; page 20, last full paragraph; and the paragraph bridging pages 20 and 21 and footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO BD> APP>& Inter. 1992).
>
> Isolation, purification, formulation, and delivery of proteins represent significant challenges to pharmaceutical scientists, as proteins possess unique chemical and physical properties. These properties pose difficult stability problems (Abstract). With the recent advances in recombinant DNA technology, the commercial production of proteins for pharmaceutical purposes has become feasible. [] Unfortunately, proteins possess chemical and physical properties which present unique difficulties in the purification, separation, storage, and delivery of these materials. (Manning et al., Pharmaceutical Research, p. 903).

The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art.

In re Buchner 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification does not teach how to use any of the HJ loop peptide derivatives, or whether any of the peptides can actually be used, to modulate the activity of a serine/threonine kinases in a subject. The specification and claims have described specific sequences (namely 25 sequences distinctly claimed, SEQ ID NOS: 2-7, 12-19, 20-22, 63-64, and 66-68) and proposed other derivatives (i.e. substations/fragments thereof), as *proposed* peptides capable of modulating serine/threonine kinase in a subject. Only six sequences have been tested for modulating serine/threonine IN VITRO [SEQ ID NO: 13 (JH38), 14, (J41), **15 (J42), 16 (J43) [all in Example 2];** 24 [Example 3]; and 47 [Example 4]]; BUT NOT "in a subject"; has not enabled ANY peptide sequences or derivatives for modulating serine/threonine activity "in a subject" – the claimed invention.

SEQ ID NOS: 13-16, which are claimed (13 and 14 have similar residues and 15 and 16 have similar residues) are described as capable of inhibiting proliferation of bovine aortic cells and the transformed mouse cell lines MS1 and SVR (page 29). However, *these have only been tested in vitro in cell culture*, not "*in a subject*". Applicant does not postulate what these sequences may be useful for "in a subject".

The other two sequences, SEQ ID NOS: 24 (Example 3) and 47 (Example 4), which are not claimed, were described to inhibit collagen formation and change morphology of B16 melanoma cells, respectively. However, *these have only been tested in vitro in cell culture*, not "*in a subject*". Applicant only postulates that "in a subject" these two SEQ ID NOS: "might be useful" for inhibition of scar formation or as anti-tumor agents, respectively (page 30-31).

The specification has not defined how it is known that these derivative peptides are capable of modulating such activity "in a subject".

The breadth of the claims and the quantity of experimentation needed: The claims are drawn to a substantially broad range of peptide derivatives contemplated as capable of use in a subject for modulating serine/threonine kinase. As Rudikoff et al. teach, a single amino acid substitution (equally applicable to a deletion in the case of fragments of the HJ loop) may be enough to alter peptide specificity or function. Furthermore, Benet and Manning both teach the difficulties of using peptides in a subject, even if a peptide is capable of function in vitro. Absent sufficient teachings in the specification to overcome the teachings of unpredictability found in the art; namely as to how it is known that these peptide derivatives will modulate serine/threonine activity "in a subject", and absent any evidence of trials conducted on "subjects", it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112 1st Scope

Claims 1-39 and 42-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being potentially enabling for the use of six sequences in modulating serine/threonine IN VITRO [SEQ ID NO: 13 (JH38), 14, (J41), **15 (J42), 16 (J43) [all in Example 2];** 24 [Example 3]; and 47 [Example 4]]; BUT NOT "in a subject"; has not enabled ANY peptide sequences or derivatives for modulating serine/threonine activity "in a subject" – the claimed invention. Furthermore, SEQ ID NOS: 42 and 43 have not even been claimed. Thus, the claimed invention has not been shown to be enabled for ANY of the claimed peptide sequences, because none of the sequences have been tested in vivo (i.e. in a subject). The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to use the invention commensurate in scope with these claims. See MPEP § 2164.08.

The nature of the invention; The state of the prior art and the predictability or lack thereof in the art; and The amount of direction or guidance present and the presence or absence of working examples have all been discussed above.

The breadth of the claims and the quantity of experimentation needed:

As discussed above, the claims are drawn to a substantially broad range of peptide derivatives contemplated as capable of use in a subject for modulating serine/threonine kinase. As Rudikoff et al. teach, a single amino acid substitution (equally applicable to a deletion in the case of fragments of the HJ loop) may be enough to alter peptide specificity or function. Furthermore, Benet and Manning both teach the difficulties of using peptides in a subject, even if a peptide is capable of function in vitro. Absent sufficient teachings in the specification to overcome the teachings of unpredictability found in the art; namely as to how it is known that these peptide derivatives will modulate serine/threonine activity "in a subject", and absent any evidence of trials conducted on "subjects", it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

As discussed at the outset, *in order to move the prosecution forward*, this Examiner has searched and herein examined claimed SEQ ID NOS: 15-19 (5) (claim 49), as drawn to the elected invention Group III, since these five sequences were found to have a recognizable core sequence. However, as discussed above, **SEQ ID NOS: 15 (J42) and 16 (J43) [Example 2]** have been tested, of these five sequences, and only in vitro. It is suggested that *Applicant*

provide where support/enablement for use of these sequences to modulate serine/threonine activity "in a subject", can be found in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-39 and 42-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 42, it is unclear what a "therapeutically effective amount" constitutes? It is suggested that Applicant distinctly claim what "therapeutically effective amount" is used.

Allowable Subject Matter

Notwithstanding the rejections above, as to the use of these sequences, SEQ ID NOS: 15-19 (5) were found to be free of the prior art, following search/analysis of the sequence results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 703-305-5039. The examiner can normally be reached from 7:00 AM – 5:30 PM, off Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-1234 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

MA
November 14, 2003

CHRISTOPHER R. TATE
PRIMARY EXAMINER